

Response Under 37 CFR 1.116

Expedited Procedure

Examining Group 1618

Application No. 10/564,372

Paper Dated: November 23, 2010

In Reply to USPTO Correspondence of August 23, 2010

Attorney Docket No. 4385-053939

AMENDMENTS TO THE DRAWINGS

The attached NEW SHEET of drawings includes Figs. 1a and 1b, which were originally included in the text of the specification at page 3. The Examiner requested that these figures be included in the drawings, rather than in the text of the specification.

Attachment: One NEW SHEET

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REMARKS

Claims 7-16 are currently pending in this application. Claims 1-6 were cancelled, without prejudice.

At pages 8-9 of the Office Action, the disclosure was objected to because of the following alleged informalities: the presence of embedded figures, viz., Figs. 1a and 1b on page 3. The Office Action requested submission of a new drawing sheet containing Figs. 1a and 1b and deleting the figures from the body of the specification. Applicants have amended the specification at page 3 to delete Figs. 1a and 1b and has added Figures 1a and 1b to the drawings. Accordingly, Applicant requests that the objection be reconsidered and withdrawn.

No new matter has been added to the application by the foregoing amendments.

Claims 7-13 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Shaffner (U.S. Patent No. 5,980,573) in view of Fox, Jr. et al. (U.S. Patent No. 5,019,096) and further in view of Nies, et al. (U.S. Patent No. 5,997,544) and Kirschner et al. (U.S. Patent No. 5,942,218). The reasons for rejection are set forth in the Office Action at pages 2-8. For brevity, these reasons for rejection are not repeated but are incorporated by reference herein.

Applicants respectfully traverse the §103(a) rejection and request that the rejection be reconsidered and withdrawn.

As reiterated by the Supreme Court in *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 82 U.S.P.Q.2d 1385 (2007), the framework for the objective analysis for determining obviousness under 35 U.S.C. §103 is stated in *Graham v. John Deere*. Examination Guidelines for Determining Obviousness Under 35 U.S.C. 103 in View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.*, 72 Fed. Reg., No. 195 (October 10, 2007) at page 57527 (hereinafter "Examination Guidelines"). The factual inquiries enunciated by the Court are as follows:

- (1) Determining the scope and content of the prior art;
- (2) Ascertaining the differences between the claimed invention and the prior art; and
- (3) Resolving the level of ordinary skill in the pertinent art.

Examination Guidelines at page 57527.

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To refute this obviousness rejection, Applicants respectfully submit herewith the Declaration of Mr. Frank Schilke (hereinafter "Schilke Declaration"). Mr. Schilke is a co-inventor of the invention disclosed and claimed in the subject patent application, U.S. Patent Application Serial No. 10/564,372. Schilke Declaration at paragraph 1.

Since receiving a degree in Chemistry (degree as Diplomchemiker, equivalent to Master of Science) at the Martin-Luther-University Halle where he studied from 1991 to 1996, Mr. Schilke has been working in the field of PMMA bone cement research for many years. Schilke Declaration at paragraph 2. Since 2006, Mr. Schilke has been an employee of Biomet Deutschland GmbH (the assignee of the present application) and has been responsible for quality control of PMMA bone cement products for Biomet Switzerland GmbH (which is a related company). Schilke Declaration at paragraph 2.

Mr. Schilke has reviewed the above-identified patent application, the pending claims thereof, the Office Action of August 23, 2010 and cited references, including the rejection of claims 7-16 under 35 U.S.C. §103(a) as being obvious over U.S. Patent No. 5,980,573 ("Shaffner") in view of U.S. Patent No. 5,019,096 ("Fox, Jr. et al.") and further in view of U.S. Patent No. 5,997,544 ("Nies et al.") and U.S. Patent No. 5,942,218 ("Kirschner et al.") as set forth in the Office Action for the above-identified patent application. Schilke Declaration at paragraph 3. Mr. Schilke has reviewed and considered the cited prior art as set forth in the Office Action, and believes that none of the cited prior art, combined as set forth in the Office Action, discloses or suggests the method of preventing microbial colonization of a bone cement surface of claim 7. Schilke Declaration at paragraph 3.

Claim 7 of the present invention relates to a method of preventing microbial colonization of a polymethyl methacrylate (PMMA) bone cement surface, comprising the step of admixing polyhexamethylene biguanide with a PMMA bone cement, wherein the active principle concentration of the polyhexamethylene biguanide is 1% or less by weight of the total amount of the PMMA bone cement.

Mr. Schilke is familiar with the disclosure of Shaffner (U.S. Patent No. 5,980,573). Schilke Declaration at paragraph 4. Shaffner relates to a prosthetic device for

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placement in an implant area of the body (Abstract). Schilke Declaration at paragraph 4. This device can be used for replacement of an implanted device in order to fight and prevent infections. Schilke Declaration at paragraph 4. Accordingly, the prosthesis comprises a material such as PMMA bone cement which is impregnated with an antibiotic (column 3, lines 54-55). Schilke Declaration at paragraph 4. In Mr. Schilke's opinion, Shaffner does not suggest or disclose use of a non-antibiotic **antiseptic** compound such as polyhexamethylene biguanide ("PHMB"). Schilke Declaration at paragraph 4.

Antibiotics, however, are known for causing resistance if used over a long time period. Schilke Declaration at paragraph 5. In contrast, antiseptics, such as PHMB, are not known to promote an increase in resistant germs. Schilke Declaration at paragraph 5. This is due to the different modes of actions of antibiotics and antiseptics. Schilke Declaration at paragraph 5. Antibiotics have a selective toxicity against specific bacteria, while antiseptics usually inhibit, but do not always kill, the growth of microorganisms. Schilke Declaration at paragraph 5.

It was an object of the present invention to replace the antibiotic in conventional bone cements with a novel medicament to prevent microbial colonization on the surface of the cement (Specification at page 2, lines 7-17). Schilke Declaration at paragraph 5. This object was solved by using PHMB. Schilke Declaration at paragraph 4. Surprisingly, PHMB was not only able to diffuse out of the bone cement, but also showed an improved antimicrobial effect. Schilke Declaration at paragraph 5.

This improved effect is shown in the diagrams of Figs. 1a and 1b, which clearly show that the use of PHMB provided an improved effect compared to the conventionally applied antibiotic gentamicin. Schilke Declaration at paragraph 5. When **0.155 %** PHMB was used, almost no colonization of the cement surface with Staphylococci was detectable even after 7 days of incubation. Schilke Declaration at paragraph 5. In contrast, when using the much larger amount of **0.86 %** gentamicin, the cement surface was strongly colonized with Staphylococci. Schilke Declaration at paragraph 5. Thus, PHMB exhibited an improved antimicrobial effect compared to gentamicin. Schilke Declaration at paragraph 5.

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In Mr. Schilke's opinion, this result was surprising and thus not predictable by a person skilled in the art. Schilke Declaration at paragraph 5.

Mr. Schilke is familiar with the disclosure of Fox Jr., et al. (U.S. Patent No. 5,019,096). Schilke Declaration at paragraph 6. This patent relates to a method of preparing an infection resistant medical device, wherein the device comprises a coating containing an antimicrobial compound (Abstract). Schilke Declaration at paragraph 6. Preferred coating materials are polyurethane, silicon or degradable polymers (col. 2, lines 12-16). Schilke Declaration at paragraph 6. A combination of a silver salt and a biguanide, in particular chlorhexidine, is used as an antimicrobial compound (column 2, lines 10 to 27). Schilke Declaration at paragraph 6.

However, chlorhexidine does not have a very good biocompatibility. Schilke Declaration at paragraph 6. The compound chlorhexidine described in **Fox et al.** is a low molecular biguanide derivative with a molecular weight of 505. Schilke Declaration at paragraph 6. It is known to use small compounds with good water solubility for obtaining an antiseptic effect on the cement surface or in the surrounding thereof, in particular due to their good diffusion properties. Schilke Declaration at paragraph 6.

In contrast, higher molecular weight compounds are usually characterized by a low diffusion rate. Schilke Declaration at paragraph 6. In such case, it had only been possible so far to increase the diffusion rate by increasing the concentration in the bone cement or to increase the permeability of the cement matrix by adding further additives or auxiliaries to the cement. Schilke Declaration at paragraph 6.

Therefore, it was completely unexpected that, by combining PMMA cement and polyhexamethylene biguanide (PHMB), the higher molecular weight PHMB was able to diffuse from the bone cement and provide long-lasting prevention of microbial colonization of the PMMA surface. Schilke Declaration at paragraph 6.

Furthermore, it was surprisingly found that very low amounts of the higher molecular weight PHMB suppressed colonization of the cement surface of the bone cement by pathogenic bacteria in an effective manner. Schilke Declaration at paragraph 6. This is even

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more surprising, since PHMB has inferior prerequisites for release from PMMA bone cement compared to the usually applied gentamicin (see Figs. 1A and 1B in the application). Schilke Declaration at paragraph 6. Due to the high molecular weight of PHMB of more than 1700, it was not expected that this substance with a low concentration of up to 1 weight% to the PMMA bone cement would be released in an effective amount during the relatively long time range of more than 7 days. Schilke Declaration at paragraph 6.

The data of Figs. 1A and 1B clearly show the diffusion of PHMB from the bone cement. Schilke Declaration at paragraph 6. If this wasn't true, no antimicrobial effect on the tested Staphylococci would be detectable. Schilke Declaration at paragraph 6. If no PHMB diffusion occurred, the number of determined germs would be the same for both plain bone cement (Palamed plain) and the PHMB containing bone cement. Schilke Declaration at paragraph 6. However, this is not the case as shown in the diagrams of Fig. 1A and 1B. Schilke Declaration at paragraph 6. Therefore, a person skilled in the art would understand that the data in Figs. 1A and 1B show diffusion of PHMB from the bone cement. Schilke Declaration at paragraph 6.

In the present invention, it has been described for the first time that the simple combination of high molecular PHMB and PMMA bone cement shows an effective antiseptic effect without any further measures. Schilke Declaration at paragraph 6. Upon information and belief, Mr. Schilke believes that the antiseptic effect of PHMB is not exclusively based on the simple release of the compound into the surrounding media and the destruction of the suspended germs, but is based upon unexpected synergy. Schilke Declaration at paragraph 6.

In fact, the surprisingly high and long-lasting effectiveness suggests an attachment or colonization of the polymeric cement surface by the released compound so that the compound is enriched on the surface in form of the thin layer. Schilke Declaration at paragraph 6. Similar observations were made in case of adhesion of polyethylene glycol (PEG) on polymeric surfaces whereby in this circumstance the similarity of PEG and PHMB in respect to some physical chemical properties has to be pointed out. Schilke Declaration at paragraph 6. Such a layer formation accounts for the unexpected effect that after incubation in a bacterial

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culture the colonization of the cement surface is effectively suppressed over a longer time period.

Schilke Declaration at paragraph 6.

Therefore, in Mr. Schilke's opinion, it was not obvious for a person skilled in the art at the time of the present invention to conclude from the application of a smaller molecule such as chlorhexidine to use a compound having a high molecular weight, such as PHMB, to achieve the unexpected high antiseptic effectiveness provided when mixing such a low amount of PHMB with PMMA bone cement. Schilke Declaration at paragraph 6. Rather, it contradicts the prevailing opinion that small, water soluble molecules are preferred for the release of compounds from solid polymeric carrier materials by matrix diffusion. Schilke Declaration at paragraph 6.

Mr. Schilke also is familiar with the teaching of Nies et al. (U.S. Patent No. 5,997,544). Schilke Declaration at paragraph 7. Nies et al. describes a process and a device for producing sterile-packed bone cement to which amongst others antibiotics can be added (column 6, lines 34 to 38). Schilke Declaration at paragraph 7.

Thus, this document discloses solely the use of antibiotics and not antiseptics like PHMB. Schilke Declaration at paragraph 7.

Kirschner et al. (U.S. Patent No. 5,942,218) relates also to an anti-infective material for treatment and/or prophylaxis of wound infections which can comprise amongst others PHMB with a mean molecular weight of 2,900 to 15,000 (col. 2, lines 52-57). Schilke Declaration at paragraph 8. This substance can be used in form of aqueous solutions, emulsions, suspensions, gels and the like for wound treatment (col. 4, lines 6 to 16). Schilke Declaration at paragraph 8.

In Mr. Schilke's opinion, Kirschner et al. does not suggest or disclose the application of PHMB in bone cement. Schilke Declaration at paragraph 8. Therefore, one of ordinary skill in the art does not get any hint from this document that PHMB would diffuse from bone cement. Schilke Declaration at paragraph 8.

In Mr. Schilke's opinion, based on the foregoing, it would not have been obvious for a person of ordinary skill in the art at the time of the present invention to apply the

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chlorhexidine described by **Fox et al.** in bone cement according to **Shaffner** or **Nies et al.** *with the aim of preventing the microbial colonization of the cement surface.* Schilke Declaration at paragraph 9.

Also, the application of the high molecular polyhexamethylene biguanide described by **Kirschner et al.** in bone cement was not obvious since it was surprising for a person skilled in the art that polyhexamethylene biguanide was released from bone cement at all. Schilke Declaration at paragraph 9. This effect is not disclosed or obvious in view of **Kirschner et al.** Schilke Declaration at paragraph 9.

For at least the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

Applicants respectfully request consideration of the Supplemental Information Disclosure Statement submitted herewith and return of an initialed SB-08a form indicating consideration and entry of the references submitted.

Conclusion

It is believed that any pending rejections have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as intent to concede any issue with regard to any claim, except as specifically stated in this paper.

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Applicants submit that the pending claims are in condition for allowance, which action is requested. The Examiner is invited to contact the undersigned directly at 412-227-3061 with any questions.

Respectfully submitted,

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